AMENDMENTS TO THE CLAIMS

1. (Currently amended) A method for associating a gene **G** in the genome of a species with a clinical trait **T** exhibited by one or more organisms in a plurality of organisms of said species, the method comprising:

(A) identifying an expression quantitative trait loci (eQTL) for said gene **G** using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for said gene **G** as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for said gene **G** in an organism in said plurality of organisms, and wherein said first QTL analysis comprises (1) testing for linkages between the plurality of expression statistics for said gene **G** and a plurality of locations along a genetic map of the plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for said gene **G** using allelic association analysis;

(B) identifying a clinical quantitative trait loci (cQTL) that is linked to said clinical trait **T** using a second QTL analysis, wherein said second QTL analysis uses a plurality of phenotypic values as a quantitative trait, wherein each phenotypic value in said plurality of phenotypic values is a phenotypic value for said clinical trait **T** in an organism in said plurality of organisms; and

(C) determining whether said eQTL and said cQTL colocalize to the same locus in the genome of said species, wherein, when said eQTL and said cQTL colocalize to the same locus, said gene **G** is deemed to be associated with said clinical trait **T**,

wherein the identifying step (A), the identifying step (B), and the determining step (C) are executed using a suitably programmed computer.

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2. (Original) The method of claim 1, wherein said determining step further comprises determining whether the locus of said eQTL in the genome of said species corresponds to the physical location of said gene **G** in the genome of said species, wherein, when said locus of said eQTL in the genome of said species corresponds to the physical location of said gene **G** in the genome of said species, the association between said gene **G** and said clinical trait **T** is confirmed.

3. (Previously presented) The method of claim 2, wherein said eQTL corresponds to the physical location of said gene **G** when the eQTL and said gene **G** colocalize within 3cM of each other in the genome of said species.

4. (Previously presented) The method of claim 2, wherein said eQTL corresponds to the physical location of said gene **G** when the eQTL and said gene **G** colocalize within 1cM of each other in the genome of said species.

5. (Original) The method of claim 1, wherein said eQTL and said cQTL are not colocalized unless a test for pleiotropy indicates that said eQTL and said cQTL are represented by a QTL that is common to both said eQTL and said cQTL.

6. (Original) The method of claim 1, wherein said first QTL analysis and said second QTL analysis each uses a genetic map.

7. (Previously presented) The method of claim 6, which further comprises, prior to execution of the identifying step (A), a step of constructing said genetic map from a set of genetic markers associated with said plurality of organisms.

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8. (Original) The method of claim 7, wherein said set of genetic markers comprises single nucleotide polymorphisms (SNPs), microsatellite markers, restriction fragment length polymorphisms, short tandem repeats, DNA methylation markers, sequence length polymorphisms, random amplified polymorphic DNA, amplified fragment length polymorphisms, or simple sequence repeats.

9. (Original) The method of claim 7, wherein genotype data is used in said constructing step and wherein said genotype data comprises knowledge of which alleles, for each marker in said set of genetic markers, are present in each organism in said plurality of organisms.

10. (Original) The method of claim 7, wherein said plurality of organisms represents a segregating population and pedigree data is used in said constructing step, and wherein said pedigree data shows one or more relationships between organisms in said plurality of organisms.

11. (Original) The method of claim 10, wherein said plurality of organisms comprises an F2 population, a F_t population, a $F_{2:3}$ population, or a Design III population and said one or more relationships between organisms in said plurality of organisms indicates which organisms in said plurality of organisms are members of said F2 population, said F_t population, said $F_{2:3}$ population, or said Design III population.

12. (Original) The method of claim 1, wherein each said expression value is a normalized expression level measurement for said gene **G** in an organism in said plurality of organisms.

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13. (Original) The method of claim 12, wherein each said expression level measurement is determined by measuring an amount of a cellular constituent that corresponds to said gene **G** in one or more cells from an organism in said plurality of organisms.

14. (Original) The method of claim 13, wherein said amount of said cellular constituent comprises an abundance of an RNA present in said one or more cells of said organism, an abundance of a protein in said one or more cells of said organism, an abundance of an mRNA expressing said gene, or a degree of protein modification.

15. (Previously presented) The method of claim 14, wherein said amount of said cellular constituent comprises an abundance of an RNA present in said one or more cells of said organism, and wherein said abundance of said RNA is measured by a method comprising contacting a gene transcript array with said RNA from said one or more cells of said organism, or with nucleic acid derived from said RNA, wherein said gene transcript array comprises a positionally addressable surface with attached nucleic acids or nucleic acid mimics, wherein said nucleic acids or nucleic acid mimics are capable of hybridizing with said RNA, or with nucleic acid derived from said RNA.

16. (Original) The method of claim 12, wherein said normalized expression level measurement is obtained by a normalization technique selected from the group consisting of Z-score of intensity, median intensity, log median intensity, Z-score standard deviation log of intensity, Z-score mean absolute deviation of log intensity, calibration DNA gene set, user normalization gene set, ratio median intensity correction, and intensity background correction.

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17. (Previously presented) The method of claim 1, wherein said first QTL analysis comprises:

(i) testing for linkage between (a) the genotypes of said plurality of organisms at a position in the genome of said species and (b) said plurality of expression statistics for said gene **G**;

(ii) advancing the position in said genome by an amount; and

(iii) repeating steps (i) and (ii) until all or a portion of the genome of said species has been tested.

18. (Original) The method of claim 17, wherein said amount is less than 100 centiMorgans.

19. (Original) The method of claim 17, wherein said amount is less than 10 centiMorgans.

20. (Original) The method of claim 17, wherein said amount is less than 5 centiMorgans.

21. (Original) The method of claim 17, wherein said amount is less than 2.5 centiMorgans.

22. (Canceled)

23. (Previously presented) The method of claim 17, wherein said testing (i) generates a statistical score for said position in the genome of said species.

24. (Previously presented) The method of claim 23, wherein said testing (i) is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

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25. (Original) The method of claim 24, wherein said eQTL is represented by a lod score that is greater than 2.0.

26–27. (Canceled)

28. (Original) The method of claim 24, wherein said eQTL is represented by a lod score that is greater than 5.0.

29. (Previously presented) The method of claim 1, wherein said second QTL analysis comprises:

(i) testing for linkage between (a) the genotypes of said plurality of organisms at a position in the genome of said species and (b) said plurality of phenotypic values;

(ii) advancing the position in said genome by an amount; and

(iii) repeating steps (i) and (ii) until all or a portion of the genome of said species has been tested.

30. (Original) The method of claim 29, wherein said amount is less than 100 centiMorgans.

31–32. (Canceled)

33. (Original) The method of claim 29, wherein said amount is less than 2.5 centiMorgans.

34. (Canceled)

35. (Previously presented) The method of claim 29, wherein said testing (i) generates a statistical score for said position in the genome of said species.

36. (Previously presented) The method of claim 35, wherein said testing (i) is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

37. (Original) The method of claim 36, wherein said cQTL is represented by a lod score that is greater than 2.0.

38–39. (Canceled)

40. (Original) The method of claim 36, wherein said cQTL is represented by a lod score that is greater than 5.0.

41. (Previously presented) The method of claim 1, wherein said species is human.

42. (Original) The method of claim 1, wherein said clinical trait **T** is a complex trait.

43. (Original) The method of claim 42, wherein said complex trait is characterized by an allele that exhibits incomplete penetrance in said species.

44. (Original) The method of claim 42, wherein said complex trait is a disease that is contracted by an organism in said population, and wherein said organism inherits no predisposing allele to said disease.

45. (Original) The method of claim 42, wherein said complex trait arises when any of a plurality of different genes in the genome of said species is mutated.

46. (Original) The method of claim 42, wherein said complex trait requires the simultaneous presence of mutations in a plurality of genes in the genome of said species.

47. (Original) The method of claim 42, wherein said complex trait is associated with a high frequency of disease-causing alleles in said species.

48. (Original) The method of claim 42, wherein said complex trait is a phenotype that does not exhibit Mendelian recessive or dominant inheritance attributable to a single gene locus.

49. (Original) The method of claim 42, wherein said complex trait is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine, nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriases, schizophrenia, or xeroderma pigmentosum.

50. (Original) The method of claim 1, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 40 cM of the physical location of the cQTL in said genome.

51. (Canceled)

52. (Original) The method of claim 1, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 10 cM of the physical location of the cQTL in said genome.

53. (Original) The method of claim 1, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 6 cM of the physical location of the cQTL in said genome.

54. (Currently amended) A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism for associating a gene **G** in the genome of a species with a clinical trait **T** exhibited by one or more organisms in a plurality of organisms of said species, the computer program mechanism comprising executable instructions for performing a method comprising:

(A) identifying an expression quantitative trait loci (eQTL) for said gene **G** using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for said gene **G** as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for said gene **G** in an organism in said plurality of organisms, and wherein said first QTL analysis comprises (1) testing for linkages between the plurality of expression statistics for said gene G and a plurality of locations along a genetic map of the plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for said gene **G** using allelic association analysis;

(B) identifying a clinical quantitative trait loci (cQTL) that is linked to said clinical trait **T** using a second QTL analysis, wherein said second QTL analysis uses a plurality of phenotypic values as a quantitative trait, wherein each phenotypic value in said plurality of phenotypic values represents a phenotypic value for said clinical trait **T** in an organism in said plurality of organisms; and

(C) determining whether said eQTL and said cQTL colocalize to the same locus in the genome of said species, wherein, when said eQTL and said cQTL colocalize to the same locus, said gene **G** is deemed to be associated with said clinical trait **T**.

55–106. (Canceled)

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107. (Currently amended) A computer system for associating a gene **G** in the genome of a species with a clinical trait **T** exhibited by one or more organisms in a plurality of organisms of said species, the computer system comprising:

a central processing unit;

a memory, coupled to the central processing unit, the memory storing one or more programs that cause the central processing unit to perform a method comprising:

(A) identifying an expression quantitative trait loci (eQTL) for said gene **G** using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for said gene **G** as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for said gene **G** in an organism in said plurality of organisms, and wherein said first QTL analysis comprises (1) testing for linkages between the plurality of expression statistics for said gene **G** and a plurality of locations along a genetic map of the plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for said gene **G** using allelic association analysis;

(B) identifying a clinical quantitative trait loci (cQTL) that is linked to said clinical trait **T** using a second QTL analysis, wherein said second QTL analysis uses a plurality of phenotypic values as a quantitative trait, wherein each phenotypic value in said plurality of phenotypic values represents a phenotypic value for said clinical trait **T** in an organism in said plurality of organisms; and

(C) determining whether said eQTL and said cQTL colocalize to the same locus in the genome of said species, wherein, when said eQTL and said cQTL colocalize to the same locus, said gene **G** is deemed to be associated with said clinical trait **T**.

108–251. (Canceled)

252. (Original) The method of claim 1, the method further comprising:

(D) validating said association between said gene **G** and said clinical trait **T** by testing for genetic linkage between said expression quantitative trait loci (eQTL) and said clinical quantitative trait loci (cQTL).

253. (Original) The method of claim 252 wherein said testing for genetic linkage comprises marker-difference regression or a multiple-trait extension of composite interval mapping.

254–257. (Canceled)

258. (Original) The method of claim 5 wherein said test for pleiotropy comprises comparing a null hypothesis, indicating that said eQTL and said cQTL are represented by a QTL that is common to both said eQTL and said cQTL, to an alternative hypothesis, indicating linkage disequilibrium.

259. (Currently amended) The method of claim 258 wherein said null hypothesis is:

$$\begin{pmatrix}\gamma_1\\ \gamma_2\end{pmatrix}=\begin{pmatrix}\mu_1\\ \mu_2\end{pmatrix}+\begin{pmatrix}\beta_1\\ \beta_2\end{pmatrix}Q+\begin{pmatrix}\varepsilon_1\\ \varepsilon_2\end{pmatrix},$$

wherein

γ_1 and γ_2 represent quantitative trait random variables;

Q categorically indicates the genotype at the position of said eQTL and said cQTL in said plurality of organisms;

$\begin{pmatrix}\varepsilon_1\\ \varepsilon_2\end{pmatrix}$ has a bivariate normal random distribution with mean $\begin{pmatrix}0\\ 0\end{pmatrix}$ and covariance matrix $\begin{pmatrix}\sigma_1^2 & \sigma_1\sigma_2\\ \sigma_2\sigma_1 & \sigma_2^2\end{pmatrix}$; and

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μ_i and β_i are model parameters.

260. (Currently amended) The method of claim 258 wherein the alternative hypothesis is:

$$\begin{pmatrix}\gamma_1\\ \gamma_2\end{pmatrix}=\begin{pmatrix}\mu_1\\ \mu_2\end{pmatrix}+\begin{pmatrix}\beta_1 & \beta_2\\ \beta_3 & \beta_4\end{pmatrix}\begin{pmatrix}Q_1\\ Q_2\end{pmatrix}+\begin{pmatrix}\varepsilon_1\\ \varepsilon_2\end{pmatrix},$$

wherein

γ_1 and γ_2 represent quantitative trait random variables;

Q_1 and Q_2 categorically indicate the genotypes at the position of said eQTL and said cQTL, respectively, in said plurality of organisms;

$\begin{pmatrix}\varepsilon_1\\ \varepsilon_2\end{pmatrix}$ has a bivariate normal random distribution with mean $\begin{pmatrix}0\\ 0\end{pmatrix}$ and covariance matrix $\begin{pmatrix}\sigma_1^2 & \sigma_1\sigma_2\\ \sigma_2\sigma_1 & \sigma_2^2\end{pmatrix}$; and

μ_i and β_i are model parameters.

261. (Currently amended) The method of claim 258 wherein the alternative hypothesis is:

$$\begin{pmatrix}\gamma_1\\ \gamma_2\end{pmatrix}=\begin{pmatrix}\mu_1\\ \mu_2\end{pmatrix}+\begin{pmatrix}\beta_1 & \beta_2\\ \beta_3 & \beta_4\end{pmatrix}\begin{pmatrix}Q_1\\ Q_2\end{pmatrix}+\begin{pmatrix}\varepsilon_1\\ \varepsilon_2\end{pmatrix},$$

wherein

γ_1 and γ_2 represent quantitative trait random variables;

Q_1 and Q_2 categorically indicate the genotypes at the positions of said eQTL and said cQTL, respectively, in said plurality of organisms;

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$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ has a bivariate normal random distribution with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$;

μ_i and β_i are model parameters; and

one of conditions (i) through (iv) is valid:

(i) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 = 0$, and $\beta_3 = 0$;

(ii) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 \neq 0$, and $\beta_3 = 0$;

(iii) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 = 0$, and $\beta_3 \neq 0$; and

(iv) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 \neq 0$, and $\beta_3 \neq 0$;.

262 (Original) The method of claim 258 wherein the negative loglikelihood for the null hypothesis and the alternative hypothesis are minimized using maximum likelihood analysis thereby forming a likelihood ratio test statistic.

263–272. (Canceled)

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